

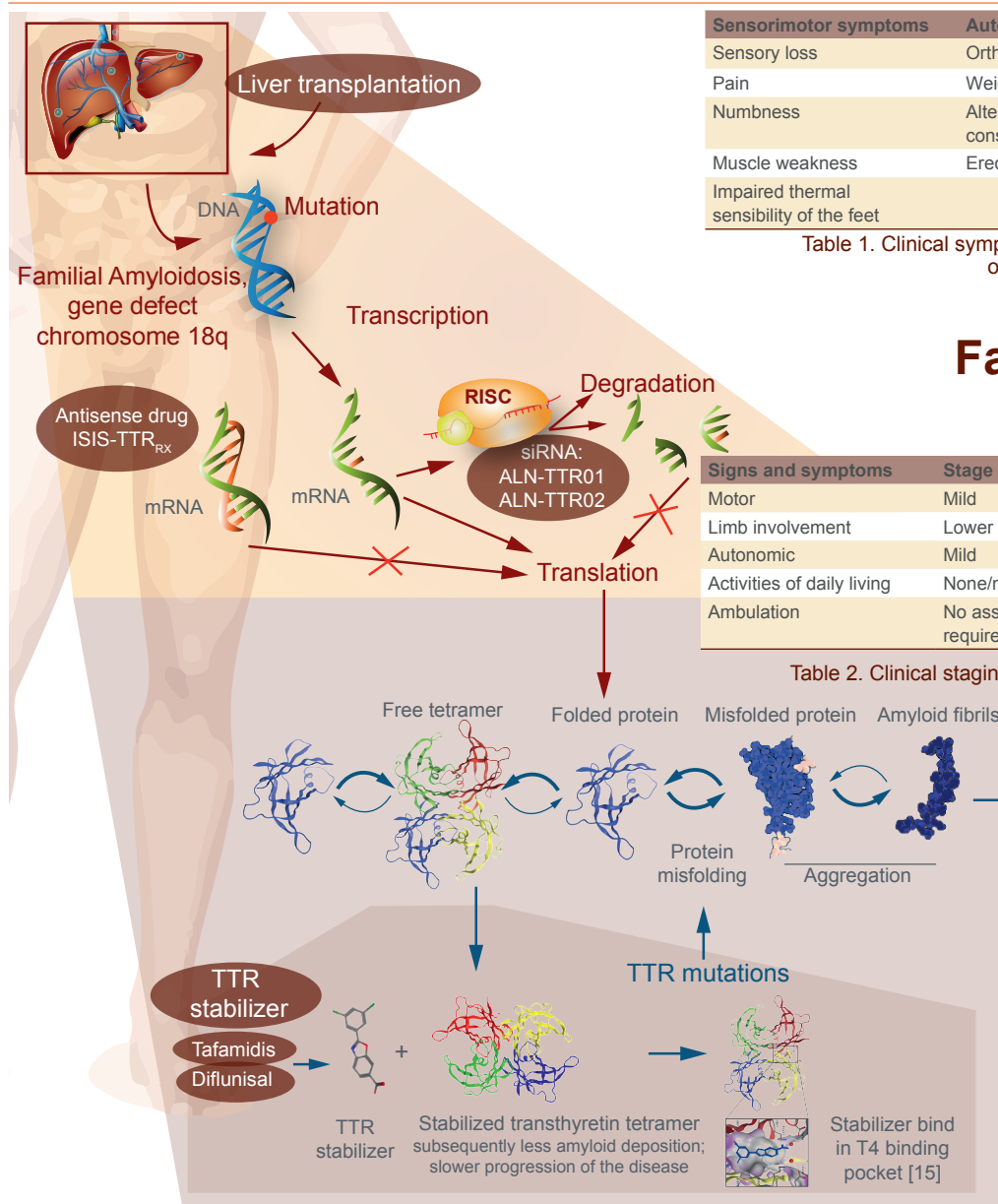
Hepatology Snapshot:



Familial amyloidosis: Great progress for an orphan disease

Ana Paula Barreiros^{1,2,*}, Gerd Otto³, Bitka Kahlen¹, Andreas Teufel^{1,2}, Peter R. Galle¹¹Department of Internal Medicine I, Universitätsmedizin der Johannes Gutenberg-University Mainz, Germany;²Department of Internal Medicine I, Universitätsklinikum der Universität Regensburg, Germany;³Department of Hepatobiliary and Transplantation Surgery, Universitätsmedizin der Johannes Gutenberg-University Mainz, Germany.

*Corresponding author. Address: Universitätsklinikum Regensburg, Department of Internal Medicine I, Franz-Josef-Strauss Allee 11, 93053 Regensburg, Germany. Tel.: +49 941-944-7021. E-mail address: Ana.Barreiros@ukr.de (A. P. Barreiros).



Sensorimotor symptoms	Autonomic symptoms	Cardiac symptoms
Sensory loss	Orthostatic disorder	Arrhythmia
Pain	Weight loss	Heart blocks
Numbness	Alternating diarrhoea and constipation	Cardiac insufficiency
Muscle weakness	Erectile dysfunction	
Impaired thermal sensibility of the feet		

Table 1. Clinical symptoms of TTR-FAP, sensorimotor symptoms occur in general in an early stage of disease

Familial amyloidosis

Signs and symptoms	Stage 1	Stage 2	Stage 3
Motor	Mild	Mild/moderate	Severe
Limb involvement	Lower	Lower/upper	Lower/upper
Autonomic	Mild	Moderate	Severe
Activities of daily living	None/minimal	Significant	Profound
Ambulation	No assistance required	Assistance required	Wheelchair/bed-bound

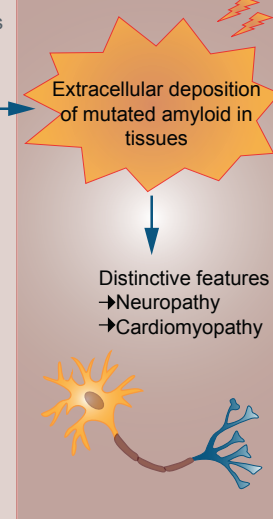
Table 2. Clinical staging system as described by Coutinho *et al.* [3]

Table 3. Overview treatment and clinical trials in FAP

Treatment	Mode of action	Type of clinical trial	Administration	Dosage	No. of patients	Included mutations	Authorization	Ref.
Tafamidis	TTR stabilizer	Phase III through 2009	p.o.	20 mg daily	128	Val30Met	yes, EMA	[11]
Diflunisal	TTR stabilizer phase II/III through 2012		p.o.	250 mg twice/day	130		no	[12]
siRNA	Gene silencing	Phase III current	i.v.	n.a.	n.a.	n.a.		
		Phase I/II through 2012	i.v.	ALT-TTR01: 0.01-1 mg per kg body weight; ALN-TTR02: 0.01-0.5 mg per kg body weight	49	Val30Met, Ser77Tyr, Ser77Phe	no	[14]
ISIS-TTR _{RX}	Antisense oligonucleotide	Preclinical	s.c.					
		Phase I current	s.c.	n.a.	n.a.	n.a.	no	[13]

p.o.: per oral; i.v.: intravenously; s.c.: subcutaneously; n.a.: not analysed; EMA: European Medical Authority



Keywords: Familial amyloidosis; Liver transplantation; Tafamidis; Pharmacological therapy.

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Hepatology Snapshot

Familial amyloidosis (synonym for familial amyloid polyneuropathy [FAP]) is an autosomal dominant inherited disease, caused by mutations in the transthyretin (TTR) gene, coding for the corresponding protein consisting of 127 amino acids. It was first described by the Portuguese neurologist Andrade. The TTR gene is located on chromosome 18q. More than 100 different mutations are known. The most common mutation is the Val30Met mutation, endemically found in Portugal, Sweden, and Japan. Among the other mutant proteins that are of etiological importance but are very rare, is apolipoprotein I and II, or fibrinogen A. Transthyretin is a tetramer, built out of four identical TTR-subunits [1]. Point mutations of the gene lead to a destabilization of the protein and subsequently to protein misfolding, resulting in the extracellular deposition of mutated amyloid in several tissues, predominantly in peripheral/autonomic nerves, gastrointestinal tract and myocardium [2].

The onset of symptoms is highly variable, depending on the underlying mutation, and occurs between 25 and >50 years. Regarding the course of the disease, patients with an early-onset have to be distinguished from late-onset patients, predominantly living in non-endemic countries like France, UK or Germany. The most common clinical symptoms are given in Table 1. Coutinho et al. established a staging system with three stages of the disease depending on the progression of walking disability and immobility [3] (Table 2). This scoring system fits predominantly for patients with an early-onset of disease. Patients with a late-onset of FAP show a more rapid progression, more functional impairment and lower survival. The prognosis of FAP is dismal and, if left untreated, results in death within 10 years after diagnosis [4]. Diagnosis of amyloidosis is most frequently performed histologically by detecting amyloid deposits in various tissues by Congo red staining following immunohistochemistry and genetic testing of the TTR gene.

Therapy of FAP

Therapy is complex and needs a multidisciplinary approach, as clinical symptoms are very heterogeneous, depending on the underlying mutation and its phenotype. Besides symptomatic therapy, liver transplantation (LT) has become the ultimate disease treatment since over 95% of the TTR-amyloid is produced in the liver [5]. However, in some cases neuropathy and/or cardiomyopathy may progress even after LT [6], potentially due to the fact that once amyloid deposits have accumulated, formation of fibrils may continue from completely normal TTR (wild type TTR). Therefore, LT should be performed at an early stage of disease. Also, since outcome after transplantation depends on the general condition of the patient, LT outcome in the advanced stage of FAP, e.g. with cachexia, or cardiac impairment, remains worse [7,8]. In patients with advanced cardiac involvement or renal impairment few combined heart and liver or kidney and liver transplantations were reported [5,8,9].

Drug therapy of FAP

Stabilizer of transthyretin

Recently, the transthyretin stabilizer Tafamidis was approved by the European Medical Authority (EMA) for treatment of early stage FAP (stage 1, disease limited to lower limbs, walking without any help). Binding of Tafamidis to the T4 binding sites stabilizes the TTR-tetramer and dissociation into monomers and amyloidogenic components is impeded [10] (Fig. 1). A recent double-blind placebo-controlled multicentre study (Fx-005) showed a benefit for stage 1 patients on 20 mg Tafamidis per day with respect to neurological symptoms, total quality of life and modified body mass index, leading to a slower progression of the disease [11] within an observation period of 18 months. Although all patients were carriers of the Val30Met mutation and of predominantly Portuguese origin, the drug was approved for all TTR-mutations. Generally, Tafamidis is well-tolerated, most frequent side effects were urinary tract infections and diarrhoea. Long-term side effects or drug-drug interactions remain to be investigated. Further trials, studying an impact of Tafamidis in patients with familial amyloid

cardiomyopathy are planned. Due to the high costs of Tafamidis, treatment should be re-evaluated every 3–6 months and if symptoms progress, e.g. neuropathy or cardiopathy, discontinuation of treatment may be considered [16].

Therapeutic perspectives on the horizon

Diffunisal is a nonsteroidal anti-inflammatory agent, which stabilizes TTR tetramers by binding to their T4-binding sites. In a recently published, double-blind, placebo controlled study regarding the effect of diffunisal treatment on polyneuropathy progression [12], 130 patients with detectable peripheral or autonomic neuropathy were investigated, demonstrating a significant reduction of progression of neurological impairment and a preserved quality of life. Although not yet approved the drug may become an effective and well-tolerated treatment alternative.

Several other therapeutic options are currently investigated. ISIS-TTR_{RX} is a second generation antisense oligonucleotide inhibitor of transthyretin, which binds to the non-translated portion of the human TTR-mRNA, resulting in the degradation of TTR-mRNA. Thus, the translation of wild type and mutant TTR proteins is interrupted. Feasibility of this therapeutic approach and a significant plasma TTR protein level suppression was shown in murine and monkey models [13]. A phase I clinical trial is currently ongoing.

Two disease specific lipid nanoparticle formulations of small interfering RNAs (siRNAs), ALN-TTR01, and ALN-TTR02 interact with wild type TTR (non-mutated) and all mutated TTRs. Intriguingly, the siRNA is predominantly delivered to the liver, the site of production of amyloid. In a recent phase I study, safety and efficacy of the siRNA therapy was investigated in 32 patients and 17 healthy volunteers [14], showing a suppression of TTR by ALN-TTR01 at day 7 of 38%, compared with placebo, and a mean reduction in TTR levels for ALN-TTR02 of 57% to 67% at day 28. Overall, the concept is promising and a phase II study is currently underway. An overview of clinical trials regarding therapy in familial amyloidosis is added as Table 3 in the Snapshot

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Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Fig. 1. Familial amyloidosis gene defect on chromosome 18q.

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